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1 UNITED STATES DISTRICT COURT  
 2 SOUTHERN DISTRICT OF NEW YORK

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3 PURDUE PHARMA L.P., et al., Trial

4 Plaintiffs,

00 Civ. 8029 (SHS)

5 v.

01 Civ. 2109 (SHS)

01 Civ. 8117 (SHS)

6 ENDO PHARMACEUTICALS, INC.,

7 Defendant.

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New York, N.Y.

June 2, 2003

10:00 a.m.

8 Before:

9 HON. SIDNEY H. STEIN

District Judge

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1 (Case called)

2 THE COURT: Good morning all. This is the trial of  
3 Purdue v. Endo, three cases, 00 Civ. 8029, 01 Civ. 2109, and 01  
4 Civ. 8117.

5 I would like to handle some housekeeping matters  
6 first. The first thing, I believe I made this disclosure at  
7 the very first time we met. But just so the record is  
8 completely clear, and it is a disclosure I made at the trial of  
9 the prior case as well, an employee of Purdue Pharma formerly  
10 was an associate at my former firm, then known as Stein  
11 Zauderer Ellenhorn Frischer & Sharp. He left Stein Zauderer  
12 before I did, so my guess is that was at least ten years ago.  
13 His name is Richard Silber. I believe he is still an employee,  
14 he is an attorney, an employee of Purdue Pharma.

15 I can adopt the matters that the parties have arrived  
16 at and agreed to in the letters dated May 23 and May 31, which  
17 really are procedural matters. The May 23rd letter is from Mr.  
18 Schwartz, setting forth the fact that cross won't be limited to  
19 the scope of direct where the person would have been called by  
20 the other side. Then, no need for a subpoena for the  
21 production of employees and agents of the parties, and so  
22 forth. I have no problem with that.

23 Similarly, I have copies of letters dated May 30 and  
24 May 31, which really are letters between counsel, but they set  
25 forth agreements on similar matters, and I have no problem with

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1 THE COURT: Wait just a moment.

2 MR. FLATTMANN: Certainly.

3 THE COURT: I understand. You are talking about  
4 OxyContin. You aren't referring to the drug oxycodone but to  
5 the product, the commercial product OxyContin?

6 THE WITNESS: Yes.

7 THE COURT: All right.

8 Q. What effect would increasing the amount of oxycodone in the  
9 combination products have on the duration of pain relief that  
10 they afford?

11 A. Really very little effect. It might increase the duration  
12 a half hour or so, but not beyond that four to six-hour period.

13 Q. Why is that?

14 A. Because it is formulated in immediate-release formulations.  
15 The drug is released from the formulation and the duration is  
16 short.

17 Q. Now let me ask you a different question. What effect would  
18 increasing the amount of either aspirin or acetaminophen in  
19 these combination products have on the duration of pain relief  
20 that they afford?

21 A. Again, it might increase the duration marginally, but again  
22 not beyond six hours or so.

23 Q. Would increasing the amount of aspirin or acetaminophen in  
24 these combination products have any other effects?

25 A. Potentially, yes. These drugs, aspirin and acetaminophen

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1 have maximum or ceiling dosages that are safe to give in a 24-  
2 hour period, particularly when patients take these medications  
3 on a 24-hour basis.

4 Q. Why do they have ceiling dosages?

5 A. It is a property of their pharmacology, that there is just  
6 a dose that you can't go beyond and get additional analgesia,  
7 or pain relief.

8 Q. What happens if you go beyond the ceiling dose?

9 A. If you go beyond the ceiling dose, you don't get any  
10 benefit in terms of increasing the analgesia. You may get a  
11 slight benefit of duration. But you can put the patient at  
12 risk for kidney or liver toxicity if they take the drugs over  
13 many days or weeks.

14 Q. Does OxyContin have any effect on the liver or kidneys?

15 A. No.

16 Q. Let me ask you to please turn to your next graphic. You  
17 made reference to that this case relates to controlled-release  
18 oxycodone formulations that produce certain blood plasma  
19 concentrations of the drug at certain times. Let's start with  
20 the term "blood plasma." What is blood plasma?

21 A. "Blood plasma" refers to the liquid portion of the blood.

22 Q. How are blood plasma concentrations of a drug described?

23 A. They are described in units of concentration typically,  
24 like milligrams per milliliter or nanograms per milliliter,  
25 those names.

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1 Q. Let me ask you to please turn to your next graphic. What  
2 are you depicting here?

3 A. I am attempting to define the medical term  
4 "pharmacokinetics." One way to think about that is it is what  
5 the body does to the drug. A more precise definition is that  
6 pharmacokinetics is the blood plasma concentration of the drug  
7 in the body over time.

8 Q. You used the abbreviation "PK" on the chart. What does  
9 that stand for?

10 A. "PK" stands for pharmacokinetics.

11 Q. Let me ask you to please turn to your next graphic. Dr.  
12 Payne, what are you showing here?

13 A. An attempt to show the release of drug from a controlled-  
14 release formulation as it moves through the gastrointestinal  
15 tract.

16 Q. Could you show the video you prepared.

17 A. Yes. As the pill moves from the esophagus into the  
18 stomach, it begins to be absorbed, and the blue dots represent  
19 drug coming out of the formulation. It then moves from the  
20 stomach into the small intestinal tract. Again, the drug is  
21 released from this formulation slowly. Then, finally, the drug  
22 will move from the small intestine to the large intestine, and  
23 drug continues to be released from the formulation. So there  
24 is a continuous slow release of drug from the intestinal tract,  
25 from the stomach through the large intestine.

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1 and I had the opportunity to be part of it and I became part of  
2 it.

3 Q. What did you do after you completed your post-doc?

4 A. Well, things were really kind of just a flow over a period  
5 of years, working with the post-doctorate program for a couple  
6 of years while setting up a laboratory in Memorial  
7 Sloan-Kettering. And then, after a few years, while still  
8 maintaining the laboratory, I became much more involved in  
9 clinical studies, their design and analysis and oversight and  
10 reporting of the clinical studies that the group was doing over  
11 the period of that decade.

12 Q. What was the general subject matter of your studies at  
13 Sloan-Kettering?

14 A. These were efficacy studies, where we looked at the potency  
15 of various analgesics, we looked at their onset, the duration  
16 of effect. We looked at the blood levels of analgesics. We  
17 tried to relate blood levels to effect. I also spent some  
18 considerable time looking back at studies that had been done  
19 before I got there, as well as working with the ongoing  
20 clinical research program.

21 Q. What analgesics did you work with primarily at Sloan  
22 Kettering?

23 A. We worked with quite a few, both directly and indirectly.  
24 I don't know that I could count them on two hands or three  
25 hands or four hands. Most often, a new analgesic would be

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1 compared in our studies to morphine. So I guess in a way I  
2 learned more about morphine than I did any other particular  
3 analgesic that we were testing relative to morphine.

4 Q. Have you authored or co-authored any published papers about  
5 the treatment of pain?

6 A. Yes, I have.

7 Q. Approximately how many?

8 A. Nearly a hundred full manuscripts and nearly 200 abstracts  
9 of studies.

10 Q. Are you a named inventor on any patents besides the three  
11 patents in suit?

12 A. Yes, I am.

13 Q. Approximately how many?

14 A. I think about ten patents in addition to the three patents  
15 in suit.

16 Q. Do any of these patents involve advances in pain  
17 management?

18 A. Yes. They all do.

19 Q. When did you leave Sloan-Kettering?

20 A. I left Sloan-Kettering in September of '85.

21 Q. What did you do after you left?

22 A. I joined Purdue.

23 Q. What was your job title when you first went to Purdue?

24 A. Associate medical director.

25 Q. What were your responsibilities as associate medical

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1 director?

2 A. My initial responsibilities when I just joined Purdue was  
3 to oversee the clinical research activities involving the  
4 currently marketed opioid analgesics -- analgesics in general  
5 rather. I participated in medical education activities,  
6 particularly lecturing, and I also had responsibility for  
7 responding to medical inquiries from health professionals who  
8 were called in or wrote in with questions about pain management  
9 or analgesics.

10 Q. Has your job changed over time?

11 A. My job changed to some extent. My responsibilities for  
12 clinical research went beyond analgesics into most of other  
13 areas that we were involved in. By 1990 I had responsibility  
14 for, as the vice president of clinical research, most all of  
15 the clinical research program.

16 Q. What products, if any, did you have responsibility for when  
17 you first arrived at Purdue?

18 A. When I very first arrived, I had responsibility for MS  
19 Contin and another analgesic, a nonopioid analgesic.

20 Q. What is MS Contin?

21 A. MS Contin is controlled-release form morphine sulfate.

22 Q. Did there come a time when you proposed that Purdue develop  
23 a new controlled-release opioid analgesic?

24 A. Yes.

25 Q. Which opioid did you propose?



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1 A. Controlled-release oxycodone.

2 Q. When did you make that proposal?

3 A. Very shortly after I first arrived.

4 Q. And to whom did you make it?

5 A. Dr. Richard Sackler.

6 Q. Who was Richard Sackler?

7 A. He is one of the owners of Purdue.

8 Q. Why did you propose to develop a new opioid analgesic?

9 A. To really make up for the deficits that were obvious with  
10 MS Contin.

11 Q. What were the shortcomings of MS Contin that you were aware  
12 of?

13 A. MS Contin, while it controlled pain when dosed every 12  
14 hours in most patients, there remained to be some patients in  
15 whom you couldn't provide pain control with every 12-hour dose  
16 and you had to dose more frequently.

17 THE COURT: What year was this when you approached  
18 Richard Sackler? You said it was shortly after you --

19 THE WITNESS: Very shortly after I arrived. It was  
20 still '85.

21 Q. Was this shortcoming, in your view, a result of the  
22 morphine itself or the controlled-release nature of the  
23 morphine?

24 A. That aspects of the problem with MS Contin were due to MS  
25 Contin and the particular delivery system it was in. It was of

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1 MS Contin rather than morphine itself.

2 Q. How did you propose to address this shortcoming?

3 A. The hope was that with the right drug and the right  
4 controlled delivery system, we could have levels in blood  
5 sustained more than the levels of morphine are sustained with  
6 MS Contin dosing. The hope was that with sustaining the levels  
7 more, we could have more patients capable of being managed with  
8 every 12-hour dosing rather than more frequent dosing.

9 Q. Were there shortcomings associated with the use of MS  
10 Contin related to the morphine itself?

11 A. Yes.

12 Q. What were those?

13 A. Morphine is a difficult drug to use well. To get the dose  
14 right, it requires substantial titration, and that had become  
15 clear. Titration is not something that a lot of healthcare  
16 professionals can take the time to do; and even when they do  
17 take the time to do well, it takes time. It is something that  
18 clearly needed improving upon, if possible.

19 Part of the titration process involved side effects.  
20 So side effects were a problem clearly with morphine as well,  
21 and there was hope that we could improve upon that.

22 Q. Could you please explain to the Court what you mean when  
23 you use the word "titration."

24 A. Titration is adjusting the dose to one that provides  
25 acceptable pain control without unacceptable side effects.

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1 Q. What property of morphine, in your view, led to the need  
2 for substantial titration?

3 A. The low oral bioavailability of oral morphine.

4 Q. Briefly, what do you mean by "oral bioavailability"?

5 A. Oral bioavailability is the degree to which a drug becomes  
6 available in the bloodstream for interaction with the opiate  
7 receptors in the brain and spinal cord after it gets absorbed,  
8 after it passes through the liver and gets metabolized.

9 Q. How did you come to understand these shortcomings of MS  
10 Contin?

11 A. Over a period of years at Memorial dealing with morphine  
12 and then later on at Memorial dealing with oral morphine and  
13 eventually MS Contin in the context of that experience over  
14 that period of time, I became aware of these things.

15 Q. Why did you propose the controlled-release oxycodone  
16 product for development by Purdue?

17 A. I felt it could improve pain management, that it would be  
18 able to address, potentially if not in fact, these problems.

19 Q. How did you propose that your controlled-release oxycodone  
20 product would improve pain management?

21 A. By really a combination of the attributes of oxycodone,  
22 which were unique to oxycodone relative to other opioid  
23 analgesics, combined with a delivery system that would present  
24 the product in a certain profile in blood.

25 Q. How many different opioids did you consider before you

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1 settled on oxycodone for development?

2 A. Between 15 and 20.

3 Q. What were the properties of oxycodone that led you to  
4 select it over the other opioids that you considered?

5 A. The properties of oxycodone included the fact that there  
6 were certain things that we knew about it. It was a known  
7 entity to a certain extent. We knew that it was effective when  
8 dosed properly. We had reason to believe that it had a high  
9 oral bioavailability and a short elimination half-life. Those  
10 were among the properties.

11 Q. What are the benefits of a short elimination half-life?

12 A. What that really means, it means the drug is turned over  
13 fairly rapidly in the body and allows a doctor to determine  
14 whether or not the dose he prescribed is the right dose and to  
15 change that dose relatively quickly if needed.

16 Q. You also mention that had oxycodone had high oral  
17 bioavailability. Did you consider the relative oral  
18 bioavailability of oxycodone compared to morphine?

19 A. Yes. Yes, I did.

20 Q. I would like you to look at Plaintiff's Exhibit 1060, which  
21 is in volume 3, but we are putting it up on the screen. Is  
22 that an exhibit that you prepared?

23 A. Yes, it is.

24 Q. Please explain how the two drugs, morphine and oxycodone,  
25 compare, in your view.

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1 A. This illustrates two ways in which they differ upon  
2 comparison. As I said, morphine, over on the left, has a low  
3 oral bioavailability. We see on the axis on the left labeled  
4 "Range of Oral Bioavailability." So morphine has relatively  
5 low oral bioavailability. Oxycodone, on the other hand, has  
6 relatively high oral bioavailability. So that is one aspect in  
7 which they differ.

8 The second aspect, which is a critical one and which  
9 is an insight that is absolutely critical to the invention, is  
10 that the range around the oral bioavailability of oxycodone had  
11 to be narrower than the range around the oral bioavailability  
12 of morphine.

13 Q. What effect, if any, did you believe that these differences  
14 in oral bioavailability would have on your controlled-release  
15 oxycodone product?

16 A. I believe that in the right delivery system, controlled-  
17 release oxycodone would be able to provide for a narrower range  
18 of daily dosages.

19 Q. Was your belief part of the conventional wisdom in the  
20 field at the time?

21 A. No. No, it wasn't.

22 Q. Please explain.

23 A. While we knew that the oral bioavailability of morphine was  
24 low and there was good reason to believe that the oral  
25 bioavailability of oxycodone was high, I don't think anybody

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1 recognized at the time, certainly my literature searches did  
2 not turn it up, that the variability around oxycodone's oral  
3 bioavailability would be narrower than the range around  
4 morphine's oral bioavailability. I also think that no one  
5 thought about how this could result in narrow range of daily  
6 dosages.

7 Q. When did you have this insight with respect to narrower  
8 range of oral bioavailability and also narrower ranges of  
9 dosages to control pain?

10 A. By the time I arrived at Purdue, I had that idea.

11 Q. Did there come a time when you reviewed data that supported  
12 your insight?

13 A. Yes.

14 Q. What data did you review?

15 A. I reviewed individual patient daily dosages in patients who  
16 had been titrated with MS Contin to a daily dose that  
17 controlled pain without unacceptable side effects. These were  
18 data that Purdue had generated over a period of years that I  
19 had access to, that I began analyzing quantitatively.

20 Q. Have you prepared an exhibit to help demonstrate your  
21 analysis of this data?

22 A. Yes, I have.

23 Q. I would like you to look, please, at Plaintiff's Exhibit  
24 1061. Is this the exhibit you prepared?

25 A. Yes, it is.

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1 Q. Please explain what the data show you with respect to MS  
2 Contin.

3 A. On the x-axis, the bottom axis, we have the dosage, that  
4 is, the daily dosage. On the ordinate we have number of  
5 patients. The data that I had access to I plotted on this type  
6 of graph. What it resulted in is a distribution, frequency  
7 histogram, whatever you want to call it, a relationship that is  
8 diagrammatically illustrated here in the solid orange line  
9 labeled "MS Contin," that line showing the wide, wide range.

10 (Continued on next page)

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1 Q. What did the data show you with respect to that range?

2 A. The range was very wide. It quantitated for me what I had  
3 as an impression an idea of earlier and really made it clear,  
4 clearer, that this is an area that if improved could be a major  
5 contribution to pain management.

6 MR. FILARDI: Objection, your Honor, with regard to  
7 foundation of this exhibit. Obviously it's something we can do  
8 on cross-examination, but it might be helpful for your Honor to  
9 know what it is that's the basis for the creation of this  
10 demonstrative evidence. This is supposed to be demonstrative.

11 THE COURT: I'll let you do it on cross.

12 MR. FILARDI: Thank you.

13 MS. LORING: I'm sorry, your Honor. I didn't hear  
14 what you said.

15 THE COURT: He can do it on cross if he wishes,  
16 inquire into the basis of the demonstrative.

17 BY MS. LORING:

18 Q. Dr. Kaiko, this indicates an 8-fold range for MS Contin.  
19 Can you explain how you calculated that range?

20 A. Yes. I eliminated the extremes, the extreme 10 percent of  
21 the patients, so I was left with 90 percent of patients by  
22 eliminating the extremes in terms of the daily dose, and then I  
23 looked and saw what I had, and what I had wound up with there  
24 was an 8-fold range of daily dosages.

25 Q. What does the exhibit show with respect to controlled-



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1 release oxycodone, or your proposed controlled-release  
2 oxycodone product?

3 A. What this exhibit shows is that the controlled-release  
4 oxycodone product would have a different distribution. It  
5 would be a narrower distribution. Being narrower, it would  
6 have of course a higher peak, and an approximate 4-fold range.  
7 And this, graphed here as a dash line, this was an insight I  
8 had at this time, given the other things that I knew and the  
9 other insight I had. And the bottom line here is that the  
10 controlling oxycodone product that he envisioned that I  
11 targeted would have an approximate 4-fold range and given  
12 dosages required to control pain in about 90 percent of  
13 patients.

14 Q. What was the basis for your reaching this conclusion as to  
15 the 4-fold range for controlled-release oxycodone?

16 A. This was based again on my -- the insight that I talked  
17 about earlier, that is, the range in oral bioavailability  
18 having to be much narrower for oxycodone, as compared to the  
19 wider one for morphine, combined with the other attributes of  
20 oxycodone, the effectiveness, the short elimination half-life,  
21 and this profile of blood levels that I had in mind.

22 Q. How did you envision that this narrower rate of dosages  
23 required to control pain would affect the titration of THE  
24 proposed controlled-release oxycodone product?

25 A. That it would provide for -- there are all kinds of ways

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1 that one could express it. I chose, as an endpoint, daily dose  
2 range, but what leads into that are things like time to stable  
3 pain control and ease of titration defined a number of  
4 different ways. There are a number of different ways it could  
5 express itself.

6 Q. You stated earlier that shortly after you arrived at Purdue  
7 you told Richard Sackler of your idea, your proposal. What is  
8 your understanding of what happened after you made your  
9 suggestion to Richard Sackler?

10 A. I recall that Dr. Sackler had thought it was a good idea  
11 and he went about progressing that program.

12 Q. Did there come a time when you discussed your idea for a  
13 controlled-release oxycodone product with others at Purdue?

14 A. Yes.

15 Q. What were the circumstances of these discussions?

16 A. Those discussions were part of the routine -- I guess they  
17 were monthly at that point -- R&D meetings.

18 Q. Who attended these meetings?

19 A. Ben Oshlack, oftentimes other people from this formulations  
20 group. I always attended those. Paul Goldenheim always  
21 attended those. Richard Sackler sometimes attended those  
22 Eventually Mark Chasin attended those. Other people in  
23 non-clinical research, as well as clinical research,  
24 participated in those meetings as well.

25 Q. Who was Ben Oshlack?

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1 A. Ben Oshlack has led up the formulations group for a long  
2 time now.

3 Q. And who was Paul Goldenheim?

4 A. At that time Paul Goldenheim was a medical director.

5 Q. What did you say about your idea for a controlled-release  
6 oxycodone product?

7 A. What I tried to express very early on was that what I had  
8 in mind was a product that would have a certain profile of  
9 blood plasma concentrations over time, and what I was looking  
10 for and which I expressed early on is I wanted something with  
11 an early peak, with a peaky kind of initial profile of blood  
12 levels, rather than a flat curve. But I wanted these  
13 sustained. I wanted these sustained but yet being peaky early  
14 on.

15 Q. Was there any discussion about how to achieve the blood  
16 level profile that you envisioned for the product?

17 A. Yes. There was discussion early on about starting by  
18 matching the initial portion of the dissolution curve for MS  
19 Contin, trying to match the initial portion of the dissolution  
20 curve for MS Contin with the controlled-release oxycodone test  
21 formulations.

22 Q. What does the term "dissolution profile" mean?

23 A. "Dissolution profile" is an in vitro test that formulators  
24 often use early on in the development programs of test  
25 formulations, experimental formulations of controlled-release

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1 products. It's a benchtop way of looking at how the tablet  
2 produces drug over time in vitro.

3 Q. What was your understanding of why there was a decision  
4 made to try to match the early portion of MS Contin as a  
5 dissolution profile?

6 A. MS Contin had an early -- was early -- was peaky early on,  
7 and that part of the MS Contin averaged -- I mean, there was a  
8 lot of variability in blood levels, but it was clear that it  
9 had an early rise in blood levels. And that part of MS Contin  
10 I wanted to keep. I thought that the way to start, with an  
11 experimental Oxy -- controlled-release oxycodone formulation  
12 was to start with an experimental tablet that would match the  
13 initial portion of the dissolution curve. It made more sense  
14 than starting anywhere else.

15 Q. What happened after you explained your idea to others at  
16 Purdue?

17 A. Well, they were well accepted, and the first move and the  
18 move that made sense was that of the formulators, and they went  
19 and began formulating experimental controlled-release oxycodone  
20 tablets.

21 Q. Were you apprised of the formulators' progress in this  
22 regard?

23 A. Excuse me?

24 Q. Were you apprised of the progress of the formulators?

25 A. Yes.

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1 Q. Did there come a time when you began clinical testing of  
2 controlled-release oxycodone formulations?

3 A. Yes.

4 Q. When was that?

5 A. That was in 1987.

6 Q. What involvement if any did you have in the selection of  
7 formulations to be used in clinical studies?

8 A. I participated in the choice of experimental formulations  
9 for that initial study.

10 Q. I would like to talk now about the types of clinical  
11 studies that you've been involved with during the development  
12 of OxyContin and other drugs. Have you prepared a  
13 demonstrative exhibit describing --

14 A. Yes, I have, yes.

15 Q. -- the different categories of clinical study?

16 A. Yes.

17 Q. I'll show you Plaintiff's Exhibit 1062, which is actually a  
18 board. It's also in volume 3 of the exhibit books.

19 A. Thank you.

20 Q. Is this the board you prepared, Dr. Kaiko?

21 A. Yes, it is.

22 Q. What is the first type of study depicted on the board?

23 A. The first type of study is a single-dose study which is  
24 designed primarily to look at blood levels.

25 Q. What types of patients are these studies conducted in?

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1 A. Yes.

2 Q. Have you prepared demonstrative exhibits to demonstrate the  
3 source of some of the language from the '912 patent?

4 A. Yes.

5 Q. I would like you to look, please, at Plaintiff's exhibits  
6 1065 and 1066. These are demonstratives that are in volume 3  
7 of your book. Can you explain, please, to the Court what the  
8 highlighting is that's in both of these documents.

9 A. The highlighting in these documents show the text from my  
10 invention disclosure that is taken verbatim and incorporated  
11 into the written patent.

12 Q. And there are also some numbers in the margin. Will you  
13 please explain the significance of the numbers.

14 A. Yes. If one looks at the invention disclosure at the  
15 highlighted areas, each paragraph in that document is numbered.  
16 If you go over, then, to the '912 patent, those highlighted  
17 areas that are taken from the invention disclosure have the  
18 same number in them corresponding to the invention disclosure.

19 So while major sections of the invention disclosure  
20 are in the patent -- not in the exact same order, but we've  
21 noted them and coded them so that you can see where in fact  
22 they appear.

23 Q. Let's look back at the exhibit, the patent, which is  
24 Plaintiff's Exhibit 8. And I'm going to put on the screen  
25 column 1. I would like you to focus on lines 9 through 17.

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1 There's a reference there to "surveys of daily dosages,"  
2 "required to control pain." Do you see that?

3 A. Yes, I do.

4 Q. To what does that refer?

5 A. That refers to the survey that I described yesterday where  
6 I examined individual patient MS Contin daily dose requirements  
7 to control pain from a series of separate studies and over a  
8 period of a couple, few years, and plotted out on a  
9 distribution or frequency histogram graph the number of  
10 patients that required various doses.

11 Q. Turn now, please, to column 3. I would like you to focus  
12 on lines 33 through 40. The paragraph starts "it has now been  
13 surprisingly discovered." To what does this paragraph refer?

14 A. This paragraph again refers to my insight that a reduced  
15 range of daily dosages were required in a majority of patients  
16 as compared to twice the range with the prototype analgesic for  
17 these kinds of patients.

18 Q. Which is?

19 A. MS Contin.

20 Q. What if anything does this statement say about whether you  
21 had proved this four-fold range through clinical studies?

22 A. Nothing, in terms of scientific proof.

23 Q. At the time that the '912 patent application was filed, did  
24 you have any scientific proof that there was a reduced range  
25 with OxyContin?

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1 A. No.

2 Q. Then what was the basis for this statement?

3 A. It was based on the insights I had, combining those  
4 insights, and knowing that in the context of a certain type of  
5 controlled-release profile, with oxycodone this had to be the  
6 case.

7 Q. At the time that the application for the '912 patent was  
8 filed, did you believe that this statement was true?

9 A. Yes.

10 Q. Do you believe it today?

11 A. Yes.

12 Q. I would like you to look now at column 5 of the patent.  
13 There's a paragraph that starts at about line 5. First I would  
14 like you to focus on lines 5 to 9 and tell me what's discussed  
15 there.

16 A. What's discussed there is the fact that, at the time, in  
17 this area of controlled-release dosage forms, that provide for  
18 the 12 hours' effect, the idea that most people had was to  
19 produce that steady state of a flat, essentially a flat curve,  
20 that that was the goal. And a flat curve typically has its  
21 maximum concentration at between four and eight hours.

22 Whereas --

23 Q. Let's --

24 A. Right.

25 Q. Let's look now at the next piece of that paragraph, lines 9



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1 blood levels are more consistent. In addition to that, what  
2 this is saying is that if a doctor chooses a certain dose of  
3 OxyContin or doubles a dose of OxyContin in a particular  
4 patient, the doctor could be much more confident, five times  
5 more confident, in knowing what the concentration of drug is  
6 going to be, as compared to if he was using MS Contin.

7 Q. Are these conclusions consistent or inconsistent with your  
8 insight as to the narrower dosage range for your CR oxycodone  
9 invention over CR morphine?

10 A. It is consistent. It is a clear reflection of the  
11 invention.

12 Q. Now I would like you to look at the third full paragraph  
13 under "Conclusions," and the second sentence, which says, "The  
14 median time to achieve stable pain control was two days with  
15 both treatments, and the number of dose adjustments required  
16 and rescue medication use were similar for both drugs."

17 How does this statement affect your belief or your  
18 insight into the reduced range of dosages needed with your  
19 controlled-release oxycodone invention?

20 A. This statement does not alter my insight.

21 Q. Can you explain that, please.

22 A. Yes. Again, this study was designed with a different  
23 purpose in mind, and it was well controlled for that purpose.  
24 That purpose was determining parameters related to blood levels  
25 and their fluctuation. The study was not designed to look at

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1 this outcome of these ease of titration. It didn't have  
2 validated methods or procedures, it didn't have the appropriate  
3 treatment controls. The number of subjects were also not  
4 chosen on the basis of this kind of outcome.

5 Those in the area of analgesiology would know by the  
6 design of this study that that would be the case, and that what  
7 we are just looking at here is a characterization of what is  
8 happening with these patients before the true experiment is  
9 being done.

10 Q. I would like you to turn now to P187369, under the heading  
11 "Study Population." Tell us how many patients participated in  
12 this study.

13 A. I'm sorry. Which page?

14 Q. It is P187369. I believe the information is in the second  
15 paragraph under the heading "Study Population."

16 A. There were about 50 patients in each of the two treatment  
17 groups.

18 Q. Did you believe that about a hundred patients were  
19 sufficient to test ease of titration?

20 A. No.

21 Q. Again, how many patients would be needed?

22 A. I would estimate, without going through the calculations,  
23 that hundreds to thousands of patients would be required.

24 Q. Were you aware of these two studies, the Kalso and  
25 Mucci-LoRusso studies during at least some of the applications

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1 that led to the patents in suit?

2 A. Yes.

3 Q. Are you aware that inventors have a duty to tell the patent  
4 office about any information that they know of that is  
5 inconsistent with statements they make about their invention?

6 A. Yes.

7 Q. Did you tell the patent office about these studies?

8 A. No.

9 Q. Why not?

10 A. They didn't either prove or disprove the invention. In  
11 fact, the results from both these studies were quite consistent  
12 with my insights and the invention. The purposes for which  
13 these studies were designed, the results of these studies  
14 demonstrate, were fulfilled and quite consistent with the  
15 invention. There was nothing inconsistent to bring to  
16 anybody's attention.

17 Q. Dr. Kaiko, did you intend to deceive the patent office when  
18 you told them about your reduced range of daily dosages with  
19 your controlled-release oxycodone invention?

20 A. No.

21 MS. LORING: I have no further questions, your Honor.

22 THE COURT: Thank you. Let's take a ten-minute break.

23 (Recess)

24 THE COURT: Dr. Kaiko, before we begin

25 cross-examination, you said that, if I understood you

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1 correctly, to test ease of titration, either of these two  
2 studies that we have been talking about, the Kalso study and  
3 the other one, would require hundreds, even thousands, of  
4 participants, is that right?

5 THE WITNESS: That would be my estimate without going  
6 through the calculations, yes.

7 THE COURT: If the study group for each of them  
8 consisted of hundreds or thousands, could ease of titration be  
9 gathered from the studies as conducted? In other words, is the  
10 only thing lacking the proper number of subjects?

11 THE WITNESS: No. There are two other things that are  
12 lacking. One are control treatments. One will want to have a  
13 treatment that on one extreme and another treatment on the  
14 other extreme, two different treatments that the medical  
15 community agree have different ease of titration.

16 The ability of the study to demonstrate that there is  
17 a difference in titratability between that negative standard  
18 and that positive standard would be a measure of the  
19 sensitivity of the study. Once having established that, then  
20 you could look at the two items of interest within the study,  
21 which is ease of titration with MS Contin and OxyContin, and  
22 make statements as to whether or not the study was sensitive  
23 enough to determine whether or not differences existed.

24 So in addition to the numbers of the patients, a  
25 second issue is control treatments.

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1 Contin with experimental formulations of controlled-release  
2 oxycodone.

3 Q. Have you ever used the term, you wanted the formulators to  
4 mimic the dissolution profile of MS Contin?

5 A. That sounds familiar.

6 Q. Is this something that derives from you? You said you were  
7 the -- I don't recall your exact words but you said that you  
8 were basically the driving force, the initiator of the whole  
9 project for what eventually became OxyContin; isn't that  
10 correct?

11 A. That's correct.

12 Q. And my question to you is, do you recall in that context  
13 whether you were the first to say, at Purdue, to the  
14 formulators, people like Ben Oshlack and John Minogue, let's  
15 match the dissolution profile of MS Contin?

16 A. I recall first saying that my interest was to get a certain  
17 profile of blood levels that would result in a certain clinical  
18 outcome. And then there was discussion of how we might, or  
19 where we might start in order to achieve that end. And there  
20 was discussion amongst us -- I don't know who first mentioned  
21 it, but we talked about matching the profile, and it was  
22 suggested that the place to start might be matching part of the  
23 profile of MS Contin.

24 I matched on to the -- I, to me, my interest was, yes,  
25 it's a reasonable place to start, but to me it's most important

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1 that you match that initial part of the curve, because I was  
2 interested in getting something that had certain things in  
3 characteris -- in common with MS Contin that were things that  
4 happened early on. But I didn't want to -- I didn't want to  
5 match the complete blood level profile among other things with  
6 MS Contin.

7 Q. Well, I'm speaking of the in vitro dissolution profile of  
8 MS Contin.

9 A. Yes. We agreed that that would be a place to start. I'm  
10 not sure I was the first one to talk about matching, but when  
11 it was brought up, I said, let's match -- you know, I was  
12 interested in matching that. And we agreed that that made  
13 sense. That made sense.

14 Q. Do you know if any work was done on that, if matching,  
15 mimicking the in vitro dissolution of MS Contin was done before  
16 you arrived, in 1985, September of 1985, at Purdue?

17 A. I hadn't become aware of that until litigation.

18 Q. But you're aware of it now?

19 A. Yes.

20 Q. But whatever, let's not get bogged down in -- whatever the  
21 starting point was, is my understanding correct that the  
22 purpose at Purdue, yourself and Ben Oshlack and other people,  
23 the purpose of mimicking the profile was to cut down the number  
24 of iterations, the formulation, reformulation process, the  
25 number of iterations to arrive at a workable formulation? Is

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1 that correct?

2 A. Yes.

3 Q. And would I be correct in stating that in this case, with  
4 regard to oxycodone, there were no iterations; isn't that  
5 correct?

6 A. There were iterations in terms of the formulation  
7 certainly. Whether or not there were iterations in terms of  
8 the matching the initial part of the profile, I mean, I think  
9 they made a number of different experimental formulations  
10 within a period of time.

11 Q. Sir, isn't it true that with regard to the development of  
12 OxyContin, that is, Acrocontin oxycodone, it was not an  
13 iterative process; it was not a trial-and-error process; Purdue  
14 was lucky because you hit it on the first trial? Purdue was  
15 very lucky and you hit it on the first trial. Isn't that  
16 correct?

17 A. Purdue was lucky in the thought --

18 Q. Isn't that correct, sir?

19 A. In the term --

20 Q. Is that correct, sir?

21 A. Not as stated. It's vague as stated and I'd like to say  
22 that it's correct to the extent that the first formulation  
23 brought in demand.

24 Q. Purdue, and it's been your testimony, Purdue has been very  
25 lucky in this case because there was no iterative process in

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1 the development of Acrocontin oxycodone or OxyContin; isn't  
2 that correct?

3 A. That's correct.

4 Q. You arrived at Purdue in September of 1985. I think you  
5 signed your employment agreement September 30, 1985. Lawyers  
6 get to know that stuff on cases like this. But is that your  
7 recollection?

8 A. Yes.

9 Q. And would I be also correct in stating that it is your  
10 position, Dr. Kaiko, that you are the originator, you are the  
11 driving force, you are the source and start of the project to  
12 develop at Purdue controlled-release oxycodone?

13 A. Yes.

14 Q. Now, when you arrived at Purdue in 1985, did you in any way  
15 attempt to familiarize yourself with the prior work of Ben  
16 Oshlack and his colleagues at Purdue?

17 A. No.

18 Q. So you only realized today that in fact Oshlack and his  
19 coworkers had already started, for example, to mimic MS Contin,  
20 its profile, before you came to Purdue; isn't that correct?

21 A. No. I have no reason to believe that they ever tried to  
22 mimic MS Contin before I arrived at Purdue.

23 Q. So you haven't been shown any documents in this case that  
24 were written by Ben Oshlack with regard to MS Contin and  
25 mimicking its in vitro profile before the time you came?



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1 A. I don't recall seeing it.

2 Q. And you're aware that Mr. Oshlack will be called on behalf  
3 of your company, Purdue, to testify as the next witness in this  
4 case; are you aware of that?

5 A. Yes.

6 Q. He would be a good source to know what he did prior to the  
7 time you came; wouldn't that be correct?

8 A. Yes.

9 Q. But whatever you did, I think I understand from your  
10 testimony today that your contribution to the invention had to  
11 do with the plasma oxycodone concentrations and times and the  
12 reduction of the dosage range. And that is, in other words,  
13 quicker titration time. Is that correct?

14 A. And the rest of the clinical related information in the  
15 patents.

16 Q. Right. By the way, how did you prove -- well, I think you  
17 testified to this. Prior to the filing of your application in  
18 1992, you really had no proof, scientific proof, of any nature,  
19 as to reduction in range, ease of titration; that's correct,  
20 isn't it?

21 A. Yes.

22 Q. Now, you just mentioned, when I asked you your involvement,  
23 you said "and in addition the clinical aspect of this." And  
24 that's the purpose of your original chart, Plaintiff's Exhibit  
25 1064, which I have modified to be Defendant's Exhibit 4384.

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1 Q. Now we're back in the September 28th memorandum that you  
2 wrote. See it here. It's Defendant's Exhibit 3629. And on  
3 the second page, you write, and your counsel focused in on a  
4 few other paragraphs which I won't focus in on, but I would  
5 like to focus in on a paragraph that your counsel didn't focus  
6 in on, and that is the one that says, "I attach a copy of a  
7 draft analysis." And that analysis is attached to Defendant's  
8 Exhibit 3629. Do you see what it says there? "I attach a copy  
9 of a draft analysis plan for OC93-1001 in which Dr. Fitzmartin,  
10 Mr. Thomas, Mr. Komorowski and I attempted to deal with these  
11 issues; this is not meant to be either complete nor sufficient  
12 (let's be positively creative)." Do you see that?

13 A. Yes.

14 Q. Would I understand that at this point in time you are in  
15 fact taking the lead in attempting to prove the primary claim  
16 of ease of titration; isn't that so?

17 A. No, I wouldn't say that. What I was taking the lead in is  
18 reviewing data from studies that were already completed or  
19 planned for other purposes, designed to answer questions other  
20 than this question, and seeing what we could find in fact in  
21 those studies that was related to the invention, to see, in  
22 addition to what the study was designed to do that was  
23 consistent with the invention, such as the fluctuation and  
24 variability in study 1001, but I never believed that I could  
25 prove reduction in daily dose range on the basis of going back

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1 to these studies designed for other purposes.

2 Q. Let's go on to Defendant's Exhibit 3739. Now just stay  
3 there one moment here. 3739 has on its face the distribution  
4 list and all the people. Is this generally the people who were  
5 on the distribution list for the OxyContin project, like  
6 yourself, Innaurato, Goldenheim, Grandy, Chasin, Oshlack?

7 A. Those names you mentioned were among those who were usually  
8 involved, yes.

9 Q. And what we see here, though, is a mean entity if you will,  
10 a different entity, a non-personal entity. There's the IND/NDA  
11 file. Do you see that?

12 A. Yes.

13 Q. Were you familiar with that file at the time?

14 A. No.

15 Q. Have any reason why all of this, these internal memos, are  
16 being sent to that file?

17 A. No.

18 Q. Can we go on to the next page, please. Here is Dr. Reder,  
19 OxyContin project team. You were on that team, right? And  
20 this is May 3, 1994. And what they're talking about is a  
21 preliminary report on the OxyContin tablets investigator  
22 survey. OxyContin tablets, that's oral dose, right?

23 A. Yes.

24 Q. And OxyContin is your invention; isn't that correct?

25 A. Yes.

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1 Q. And at least at this time it appears that you are the  
2 leading promoter of the primary claim, ease of titration.  
3 Doesn't that appear to be the case to you from these documents?

4 A. That appears to be the case, yes.

5 Q. And what does Dr. Reder report, at least preliminarily at  
6 this time, May 3, 1994? "OxyContin benefits included the  
7 following: Easier titration than Duragesic (but not MS Contin  
8 or oxycodone IR)"? Do you see that? And it's the first on the  
9 benefit list. Do you see that?

10 A. Yes.

11 Q. Duragesic is the fentanyl patch?

12 A. Yes.

13 Q. Not an oral product?

14 A. No.

15 Q. So you had a benefit of ease of titration over a non-oral  
16 product, correct?

17 Correct? According to this report. There's an easier  
18 titration than the Duragesic fentanyl patch.

19 A. Yes.

20 Q. But not the oral products, like MS Contin. Correct?

21 A. That's what it says.

22 Q. OK. How about oxycodone? Is that an oral product?

23 A. Yes.

24 Q. Now, let's go to the '331 patent application.

25 A. Could I just complete my answer for a moment?

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1 Q. Answer to what?

2 A. The question. That's what it says there, but you have to  
3 appreciate, these are 11 doctors who have very limited  
4 experience with OxyContin. It's a documented anecdote of a  
5 very small number of people.

6 Q. So at least at this point in time you were very much  
7 interested in proving the primary claim, and the preliminary  
8 indication was against the primary claim, but you believe that  
9 the indication wasn't important because of the small number of  
10 doctors who were surveyed?

11 A. This is -- this opinion of 11 doctors with limited  
12 experience with OxyContin, it doesn't prove or disprove  
13 anything. It's not -- when I saw this memo, you know, frankly  
14 I had to chuckle to a certain extent, because this is not a  
15 way -- this type of survey is not a way of answering a  
16 question.

17 Q. OK. But you know this document pretty well, don't you,  
18 because if we go to the second page -- let's go to the second  
19 page of this document. And let's go down to the fifth  
20 paragraph down, maybe the first three or four lines, please,  
21 Molly.

22 You know this well enough to know exactly the number  
23 of doctors that were surveyed, and you probably know it well  
24 enough to know that 0 out of 11 felt it was easier to titrate  
25 than MS Contin, and 1 out of 11 felt it was easier to titrate

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1 than oxycodone IR tablets.

2 MR. FILARDI: No, it's the first three lines. OK.

3 Q. I'm sorry to be distracting you with that, but you see  
4 that, right? This is 0 out of 11?

5 A. I see what that is. And this is not science.

6 Q. And this is 1994, right?

7 A. Yes.

8 Q. So if we can gather up whatever we've learned at this  
9 point, 1994 in time, you've already filed your patent  
10 application on the invention in November of 1992, correct?

11 A. Yes.

12 Q. And based upon your intuitive knowledge at the time, you  
13 said that -- whatever you said about the invention, that part  
14 of the investigation was a reduction in range, ease of  
15 titration, correct?

16 A. Part of the invention was reduction to range, reduction in  
17 range.

18 Q. OK. We'll go back and see the exact language that you used  
19 in the course of time. But I want to just get fixed in our  
20 minds that as of '94, you were attempting to prove the primary  
21 claim. You thought it was imperative, but your early  
22 indications were that it may not be true. Fair?

23 A. No. Unfair. Wrong. Where we designed studies to look at  
24 tendencies of the invention, we found data consistently  
25 consistent with the invention.

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1 Q. Did that occur, start any time prior to 1997?

2 A. Yes.

3 Q. And were those data, were those reports submitted to the  
4 FDA?

5 A. They were consistent with the invention.

6 Q. Were those reports that were consistent with the invention  
7 that is surprisingly found and proven for OxyContin over MS  
8 Contin, were they submitted to the FDA?

9 A. That -- I think most of what we -- much of what we did was  
10 submitted to the FDA. We don't --

11 Q. And if it was submitted to the FDA --

12 A. There are some things that we don't submit to the FDA.

13 Q. I'm sorry. Are you finished, sir? Forgive me. I  
14 interrupted you.

15 A. Yes. Yes.

16 Q. I apologize. OK. My point is, to the extent these  
17 documents exist, would they be in the files of Purdue?

18 A. I don't know that they all would be.

19 Q. Where would they be, if not in the files of Purdue?

20 A. Not everything we did we saved.

21 Q. OK. So some things have been destroyed.

22 A. Most likely.

23 Q. OK. Now, of this portion of the documents which support  
24 the primary claim that survived destruction, do you know  
25 whether those documents, from the files of Purdue, were sent to

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1 the FDA?

2 A. I know that some were.

3 Q. And do you know of any reason why those documents have not  
4 surfaced in this case?

5 A. They have surfaced in this case.

6 Q. And your counsel will point them out if they exist. Do you  
7 think that's a reasonable assumption, prediction, what might  
8 happen on redirect examination?

9 A. I don't know, sir.

10 Q. OK. Now, let me ask you this. Were any of those materials  
11 that supported -- demonstrated that the primary claim was true,  
12 were they submitted to the U.S. Patent Office at any time?

13 A. What we had observed was not --

14 Q. No, I'm not asking about "observed." I want to know about  
15 the studies that you did or the evidence that you had that  
16 supported the primary claim ease of titration. Were they  
17 submitted, in any form -- oral, written -- to the U.S. Patent  
18 Office?

19 A. No.

20 Q. Let's go back to the '331 patent. I would like to get that  
21 up. I think it's 2044. Now, you are not an inventor on this  
22 patent, but during the course of prosecution in this case, do  
23 you recall that the claims of Oshlack and his co-inventors were  
24 rejected in view of the '598 patent and the '341 patent?

25 A. Yes.



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1 of direct.

2 MR. FILARDI: Could we get Defendant's Exhibit 2049,  
3 the patent. Specifically, column 5, lines 5 to 15.

4 Q. I would like to parse through this paragraph a little bit.  
5 Your counsel directed you, I believe, to the second part of  
6 this, but I would like to take the whole paragraph.

7 "In order to obtain a controlled-release drug dosage  
8 form having at least a 12 hour therapeutic effect, it is usual  
9 in the pharmaceutical art to produce a formulation that gives a  
10 peak plasma level of the drug between about 4-8 hours after  
11 administration (in a single dose study)."

12 Do you see that?

13 A. Yes.

14 Q. Were you aware at that time that there were several drugs,  
15 formulations, controlled-release drug dosage formulations for  
16 moderate to strong opioid analgesics that in fact achieved a  
17 peak plasma level of between 2 to 4 hours for a 12-hour drug  
18 prior to the time this statement was made by you and your  
19 colleagues, co-inventors, in November of 1992?

20 A. Other than MS Contin, I was aware of another 12-hour  
21 release morphine product that was being characterized as having  
22 an ideal pharmacokinetic profile for 12-hourly oral  
23 controlled-release opioid for moderate to severe pain --

24 Q. Let's see if we can take this --

25 MS. LORING: Your Honor, he hasn't completed his

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1 answer.

2 A. -- and that had a Tmax that was between 4 and 8 hours. I  
3 think the only other one I was familiar with was the twice-a-  
4 day hydromorphone product that is in that category of drugs  
5 that you had made reference to. So that is what I was aware of  
6 at the time.

7 Q. Did you have a hand in writing or giving input to the  
8 writing of this particular representation to the patent office  
9 and communicating to the patent office that it is usual in the  
10 pharmaceutical art prior to your invention that to produce a  
11 formulation that gives you a 12-hour drug, you've got to have a  
12 peak plasma level of drug between 4 and 8 hours? Was that you  
13 who gave that information to the patent lawyers?

14 A. When I received the draft patent, I discussed various  
15 portions of it with outside patent counsel, and changes were  
16 made, including changes in this section. I recall how people  
17 felt about the early peak that MS Contin had. I knew what the  
18 conventional wisdom was at the time regarding the desire, the  
19 goal of the flattest curve possible for controlled-release drug  
20 for moderate to severe pain. And I revised this. I had input  
21 to this. Parts I agreed with, parts I didn't, and it reflects  
22 my position as it is written today.

23 Q. This is my question. Doesn't that communicate to the  
24 patent office that for a twice-a-day drug, twice-a-day daily  
25 drugs --

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1 A. Yes.

2 Q. -- in other words, at least 12-hour therapeutic effect,  
3 that in the past there was a 4- to 8-hour peak level for plasma  
4 and that was usual, isn't that correct? Isn't that what you  
5 are communicating in the application?

6 A. In the art, the goal, the conventional wisdom within the  
7 art was to produce a flat curve with a peak in the mid range of  
8 that curve. The products that I had been aware of included  
9 products that met that goal, and that is what people considered  
10 the appropriate product for the art to develop.

11 Q. That was something in the 4- to 8-hour range, isn't that  
12 correct?

13 A. Yes.

14 Q. Is it not a fact that as of the time of the filing of this  
15 application for the '912 patent and the other patents in suit,  
16 you were in fact aware that CR morphine, controlled-release  
17 morphine, in fact had a 2- to 4-hour Tmax, and that was for MS  
18 Contin, isn't that correct?

19 A. Yes.

20 Q. You in fact coauthored an article in 1986 showing that MS  
21 morphine had a 2 to 4 to give a 12-hour twice-a-day drug, isn't  
22 that correct?

23 A. Yes.

24 Q. Would it have been fair to point that out to the examiner  
25 at this time, that the closest commercial piece of prior art,

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1 MS Contin, against which you did a lot of studies and  
2 comparisons, had the same profile: It was 2 to 4 and gave a  
3 12-hour twice-a-day drug?

4 A. I disagree. We were very disappointed in MS Contin not  
5 having the sufficient data to support a 12-hour duration claim  
6 alone, that the drug couldn't perform in most all patients when  
7 dosed appropriately every 12 hours, requiring that some  
8 patients be dosed much more frequently.

9 Q. That is not what you wrote in 1986, is it? It is not what  
10 you wrote when your company was promoting MS Contin, was it?

11 A. We promoted that the majority of patients can have their  
12 pain controlled with every 12 hour dosing with MS Contin, and  
13 that is the truth and that is not inconsistent with what I just  
14 said.

15 Q. But you described it in your publication -- could we have  
16 DX2766 -- as a 2 to 4 rather than an 8, isn't that correct?

17 A. Oh, yes.

18 THE COURT: For Tmax?

19 Q. For Tmax?

20 A. Yes.

21 Q. I don't think we need that then.

22 Let's go on to the controlled-release codeine. Isn't  
23 it a fact that you knew Tmax was 2 to 4 for controlled-release  
24 codeine as early as 1988, several years before the 1992  
25 representation in your patent? Isn't that correct?

363rpur6

Kaiko - cross

1 A. MS Contin is --

2 Q. I am not talking about MS Contin. I am talking about CR  
3 codeine, controlled-release codeine.

4 A. That is not appropriate for moderate to severe pain.

5 Q. I'm sorry. Forgive me. I missed what you said. It is not  
6 appropriate for?

7 A. I don't think that falls within the group of drugs where  
8 you first asked the question and characterized them as drugs  
9 for moderate to severe pain. That does not fall within those.

10 Q. Let's take a look at what you wrote in your patent  
11 application.

12 MR. FILARDI: Can we go back to the patent  
13 application, please, column 5, 5 to 15. DX-2049, column 5,  
14 lines 5 to 15.

15 Q. Here you don't make a distinction based upon level of pain,  
16 do you. You say, in order to obtain a controlled-release drug  
17 dosage form having a 12 hour, it is usual in the pharmaceutical  
18 art to produce a formulation that gives a peak plasma level,  
19 Tmax, of 4 to 8 after administration. It says nothing about  
20 moderate to strong pain or anything like that.

21 A. Elsewhere in the specifications I make it clear that we are  
22 talking about drugs for moderate to severe pain, and I list  
23 several candidates, and codeine is not among them.

24 Q. Certainly not in this paragraph with regard to that  
25 representation, isn't that correct?

363rpur6

Kaiko - cross

1 A. That's correct.

2 Q. But you knew more at that time in November of 1992, because  
3 you knew that controlled-release hydromorphone --

4 MR. FILARDI: Could we get Defendant's Exhibit 3282,  
5 please, at page 309298.

6 Q. Here is a final clinical report, correct, that you signed,  
7 which shows this drug, controlled-release hydromorphone, as  
8 having a Tmax between 2 to 4, isn't that correct? You knew  
9 about that?

10 A. Yes.

11 Q. You knew that in 1988, isn't that correct? 1988. Yes, I  
12 represent to you it is 1988. And you knew more than that. You  
13 knew with regard to controlled-release dihydrocodeine of the  
14 '984 patent, that it in fact was another drug that had a Tmax  
15 of 2 to 4, well prior to your patent disclosure, isn't that  
16 correct?

17 A. Another drug for more moderate pain, a drug I hadn't had  
18 any clinical experience with in terms of these studies, wasn't  
19 in my mind as I was thinking about this.

20 Q. But, Dr. Kaiko, you were filing an application claiming a  
21 controlled-release opioid for oxycodone, right?

22 A. Yes.

23 Q. Didn't you look back into the prior art disclosures with  
24 regard to the same type of formulations, controlled-release  
25 opioid analgesic formulations? That is right into the area of

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Kaiko - cross

370

1 the subject matter of this patent. You didn't think to mention  
2 that to the patent office?

3 A. I was familiar with most all of these formulations.

4 Q. Did you tell your lawyers?

5 A. My lawyers appreciated this as well.

6 THE COURT: Is this an appropriate time to end, sir?

7 MR. FILARDI: It is, your Honor.

8 THE COURT: Why don't we break now. We will pick it  
9 up tomorrow at 11:00 a.m. Thank you.

10 (Adjourned to June 4, 2003, at 11:00 a.m.)

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364APUR1

1 phone.

2 What about the alternative?

3 MR. SCHWARTZ: Video link.

4 THE COURT: A video feed that can be -- I know at 40  
5 Foley Square they have the facilities for that. I don't know  
6 at the other end; that may be the issue.

7 MR. SCHWARTZ: That's what I would suggest, your  
8 Honor, that we do it with a video feed. I've heard of that  
9 being done before and I've been involved in it myself.

10 THE COURT: Since you are asking to have me review the  
11 video, it's not as if I were reading the transcript and can do  
12 it in a shorter period of time. Since it is in real time, it  
13 would take the exact same time for me to view it as it would  
14 for you to take it. Thinking it through, then there's a  
15 problem, because the reason I'm not having trial on Friday is  
16 because I have other cases.

17 MR. SCHWARTZ: If we had a video feed we could it in  
18 regular trial time any day, Wednesday, Thursday.

19 THE COURT: Yes, but doing it at a time when I could  
20 otherwise see you, short as the trial, from the standpoint of  
21 the last day of trial. In other words, I can watch it on a  
22 Saturday or Sunday.

23 Work it out, and if you want to do it on a video feed,  
24 we'll just have to arrange it at a time when I can be watching.

25 And I guess the video feed only has to be one way.



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1 That may make it easier. I need an audio feed the other way,  
2 but I just need a video feed to me.

3 See if you can work it out.

4 MR. SCHWARTZ: OK. We'll try.

5 THE COURT: All right. Proceed.

6 MR. FILARDI: All right. Thank you.

7 CROSS EXAMINATION

8 BY MR. FILARDI: .

9 Q. Good morning, Dr. Kaiko.

10 A. Good morning.

11 Q. Let me see if we can pick up where we left off yesterday.

12 MR. FILARDI: Can you get on the screen the '912  
13 patent, Defendant's Exhibit 0249, particularly the column, the  
14 language that we were discussing in column 5, line 5.

15 Q. Do you recall our focus toward the end of the day,  
16 yesterday, was on the, if you will, the T max and the prior art  
17 at 4 to 8, whereas with the invention it was 2 to 4. Do you  
18 recall that?

19 A. Yes.

20 Q. And if I recall your testimony --

21 A. Oh, I'm sorry, no. It's 2 to 4 1/2, sir.

22 Q. OK. When you say 2 to 4 1/2, there would be some overlap  
23 actually between what you found and in the prior art, because  
24 within the 4.5, 4 1/2 hours and 4, there was an overlap with  
25 the prior art. Isn't that correct?

364APUR1

Kaiko - cross

1 A. Yes.

2 Q. And that 4 1/2 appears in claims, doesn't it?

3 A. Yes.

4 Q. And that portion is actually a capturing of the prior art,  
5 at least in that portion of the claim; isn't that correct?

6 A. I can see how you can say that to some extent.

7 Q. Now, yesterday, if I recall correctly, you testified that  
8 as of the time of filing, writing this paragraph to the patent  
9 office, you were aware that there were several  
10 controlled-release opioid analgesic formulations that actually  
11 were characterized by a T max of 2 to 4; isn't that correct?

12 A. Yes.

13 Q. And those included controlled-release codeine. Do you  
14 recall that?

15 A. Yes.

16 Q. And you were aware of that at the time. And it also  
17 included controlled-release hydromorphone; isn't that correct?

18 A. Yes.

19 Q. And controlled-release dihydrocodeine, the 984 patent.  
20 Isn't that correct?

21 A. Yes.

22 Q. And then also controlled-release morphine, the MS Contin,  
23 you were aware that that had a T max of 2 to 4 in the prior  
24 art; isn't that correct?

25 A. Yes.

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Kaiko - cross

1 Q. And significantly, the 2 to 4 of the morphine was contained  
2 in quite a bit of literature, the description of it, quite a  
3 bit of literature of the Purdue Company, your company, isn't  
4 that correct, prior to November of 1992? Isn't that correct?

5 A. Yes.

6 Q. I would like to show you an exhibit that has been marked as  
7 Defendant's Exhibit 3260. I believe it's in the book that is  
8 in front of you, but I will get it up on the screen. Maybe you  
9 are familiar with this. Are you familiar with literature like  
10 this, where MS Contin was promoted?

11 A. Yes.

12 Q. And if you were to turn to the second page of Defendant's  
13 Exhibit 3260, you would see that it's promoted as a 12-hour  
14 drug; isn't that correct? Prominently promoted as a 12-hour  
15 drug.

16 MR. FILARDI: It would be down at the bottom of the  
17 page.

18 Q. Isn't that correct?

19 A. It was promoted primarily as a 12-hour drug, yes.

20 Q. And this brochure is well prior to November of 1992, isn't  
21 it, sir?

22 A. Yes.

23 Q. This is roughly a mid 1980's brochure; is that not correct?

24 A. Yes. Also in here is acknowledgement that it's also  
25 indicated for every 8-hour dosing.

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Kaiko - cross

1 Q. So it's indicated for both 12 hours and 8 hours depending  
2 upon how you administer it?

3 A. No. It depends on whether or not the patient can be  
4 controlled every 12 hours or not.

5 Q. Let's go to the next page. It has P-041767 down at the  
6 bottom. Do you see that page?

7 A. Yes.

8 Q. And that would indicate clearly that MS Contin has a T max  
9 of 2.7. Isn't that correct?

10 A. Yes.

11 Q. What is Roxanol SR tablets?

12 A. That is a controlled-release oral morphine formulation that  
13 differs somewhat from MS Contin.

14 Q. That also has, that drug also has a T max of between 2 and  
15 4 hours; isn't that correct?

16 A. Yes, but its efficacy dynamics are quite different.

17 Q. It falls within the general purview of an opioid analgesic  
18 in the prior art controlled-release formulation?

19 A. In a general sense, but it's not as potent, and its onset  
20 of analgesia is significantly different from that of MS Contin.

21 Q. You also mentioned yesterday during the course of your  
22 testimony that one of your contributions is to focus in on  
23 early peak T max for oxycodone?

24 A. I wanted to have an early peaky profile, yes.

25 Q. Can you turn to page 041769, take a look at what in the mid

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Kaiko - cross

1 1980's your company was showing as the curve for the MS Contin  
2 tablet. Wouldn't you say that's pretty peaky?

3 A. Yes.

4 Q. Tell me about this MEAC, the minimally effective analgesic  
5 concentration. Would I be correct that this graph indicates,  
6 to anyone who sees it, anyone who reads it at the time, that  
7 roughly the MEAC, the minimally effective analgesic  
8 concentration, for MS Contin was approaching, was a little less  
9 than 15. Can we call that 14?

10 A. I wouldn't say that, no.

11 Q. And what would you say? What does this graph tell you  
12 about the MEAC?

13 A. It's in the context of the whole document such as the  
14 previous page. It's laid out there that MEAC was arrived at,  
15 and what illustrates it are the results from eight different  
16 studies utilizing variously different ways of getting in  
17 testament of MEAC and winding up with a threefold difference  
18 from about 6 to about 20 nanograms per ML.

19 So to say that the MEAC is 14, I think, is  
20 mischaracterization of the MEAC in the context of the whole  
21 document.

22 Q. In the context of this entire document, in the mid 1980's,  
23 did you, sir, have an understanding that oxycodone at that  
24 point in time was about twice as potent as MS Contin?

25 A. Yes.

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Kaiko - cross

1 asking to have any idea of whether that might be generally  
2 high, low, or right. Nor do I have the statistical skills to  
3 calculate the power of the study.

4 Q. Would you please now turn your attention to Defendant's  
5 Exhibit 4355. By the way, this -- I'll just, I'll continue.

6 4355, here again it's another portion of the Kalso  
7 study. Is that correct?

8 A. Yes.

9 Q. Submitted to the FDA. Correct?

10 A. I don't know.

11 Q. I see on the second page there's your name but there's no  
12 signature. Do you recall whether in fact this document was  
13 signed and submitted to the FDA?

14 A. I don't know.

15 Q. Look at the first page of the document, 642906. Do the  
16 dates there generally indicate -- are they accurate to your  
17 recollection as the start date, the end date, and the study  
18 report date? And I'll read those dates and ask you whether  
19 they are consistent with your recollection of the timing of the  
20 Kalso report submitted to the FDA. Start date February 22,  
21 1994; end date May 16, 1995; study report date July 29, 1996.  
22 Correct?

23 A. Maybe you misspoke or I misunderstood you, but the report  
24 date didn't start and end under those dates. They're the study  
25 dates. Those are the study dates, the time that the first

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Kaiko - cross

1 patient was dosed and the last patient was dosed.

2 Q. OK. Thank you very much. This is work that was sponsored  
3 by your company, Purdue?

4 A. Yes.

5 Q. And Purdue selected the investigator, Kalso?

6 A. Yes.

7 Q. For the study. And did your company receive regular  
8 reports as to the progress of the study as it proceeded?

9 A. Yes.

10 Q. Could you please turn to page 642954. Would I be correct  
11 in stating that that page identifies as a primary efficacy  
12 variable of the study, quote, time to achieve stable pain  
13 management, end quote?

14 A. Yes. But that doesn't say the study was designed to  
15 determine whether or not there's a difference between  
16 treatments in that regard, as I had probably said to you many  
17 times already.

18 Q. Are you finished, sir?

19 A. Yes.

20 Q. OK. Could you please now turn to page 642793. Under the  
21 heading "time to achieve stable dosing," would you turn to the  
22 last sentence. It says, "The median time to stable dosing was  
23 three days for CR oxycodone and 1.5 days for CR morphine.  
24 There was no significant difference in the time to achieve  
25 stable pain control." My question is, were you aware of that

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Kaiko - cross

1 statement as of August 18, 1996?

2 A. Yes.

3 Q. Did you make any recommendation to your patent counsel in  
4 connection with then pending applications for the patent in  
5 suit that that information be disclosed to the patent office?

6 A. No.

7 Q. Could you go to the next page. I'm sorry. It's not the  
8 next page. It's the page that bears production number 642994,  
9 page 89 of this exhibit number Defendant's 4355. Do you see  
10 this is the conclusions page; is that correct?

11 A. I'm sorry. What page are you on again?

12 Q. 642994.

13 A. Yes.

14 Q. Under the heading 8.2, the conclusions are reached as to  
15 the efficacy of OxyContin versus MS morphine. Is that correct?

16 A. Yes.

17 Q. And in there, the third line down, and I read to you, and  
18 it reads, quote, In the titration period there were no  
19 significant differences between CR oxycodone and CR morphine  
20 treatment groups with respect to the number of days required to  
21 achieve stable pain control. Did I read that correctly?

22 A. Yes.

23 Q. And as of this time, August 16, 1996, you were aware of  
24 that conclusion being reached?

25 A. Yes. But that's in the context of study, where a



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Kaiko - cross

1 knowledgeable reader will recognize a study is not designed to  
2 determine whether that's the case or not. A study is not  
3 determined to prove or disprove that. What the study was in  
4 fact designed to do, it obtained information that was  
5 consistent with the patent.

6 Q. And this information was given to the FDA?

7 A. Yes.

8 Q. And this information was not given to the patent office?

9 A. Correct.

10 Q. I turn your attention now to Defendant's Exhibit 4359 --  
11 we've already done that. Can we jump over to 4371.

12 MR. FILARDI: Your Honor, this is my last exhibit. I  
13 know it's ten after 1. Would you like me to conclude? I can  
14 conclude.

15 THE COURT: I would like you to finish -- if you're  
16 able to finish the cross, then I think you should --

17 MR. FILARDI: I'm going to --

18 THE COURT: -- take the time you need, and when you're  
19 done, cross will be finished.

20 Q. Defendant's Exhibit 4371. Do you know what this document  
21 is?

22 A. This looks like a document to a regulatory body other than  
23 the FDA. Which regulatory body that -- a non-U.S. regulatory  
24 body other than the FDA, other than one in the U.S.A. But I  
25 don't know what country it is.

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Kaiko - cross

1 Q. And this was submitted to whatever body it was submitted to  
2 in 1996?

3 A. There's a June 16, 1997 date on the lower bottom of the  
4 page I'm looking at.

5 Q. I'm sorry. June 1997. Correct. I agree. And was it  
6 submitted on or about that time?

7 A. I don't know when it was submitted. I'm reading the dates  
8 off a piece of paper.

9 Q. Could you turn now to the last exhibit, Defendant's Exhibit  
10 4145?

11 A. Yes.

12 Q. That is in fact a publication for peer review of the Kalso  
13 study. Is that not correct?

14 A. Yes. There were more than -- this is not the only  
15 publication. There was a second mentioned publication as well,  
16 of the Kalso study, by the same authors.

17 Q. OK.

18 MR. FILARDI: Your Honor, except for offering some  
19 exhibits, which I would ask if I could have the lunchtime to  
20 gather up those exhibits so we could read them into the record  
21 for admission, but I do have one, a document which was handed  
22 to me, about the Sunshine study. I don't have copies of it,  
23 but there was an issue as to date. If I may do this. I don't  
24 have copies, but I would like to put it on the screen.

25 Defendant's Exhibit 3924.